life cycle. The ability to target specific steps of replication is apparent in the myriad of novel therapies in research, such as protease inhibitors, nucleoside and non-nucleoside polymerase inhibitors, glucosidase Inhibitors, inosine monophosphate dehyrogenase (IMPDH) inhibitors, and immune modulators (Interferons and their inducers, toll-like receptor analogues, therapeutic vaccines). Combination therapies with new small molecules and peg-INF with or without ribavirin are currently being evaluated. One of the challenges of STAT-C therapy would be the prevention of the evolution of drug resistance while enhancing tolerability, decreasing treatment duration, and ultimately achieving higher sustained virologic response rates.

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30.003

Treatment of Hepatitis C in the HIV-Infected Subject

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Liver complications have emerged as an important cause of hospitalization and mortality among HIV-infected persons.[1] Anti-HCV treatment offers the opportunity to eradicate HCV, reduce the risk of disease progression and reduce liver-related deaths. These benefits are significant and provide the justification for consideration of HCV treatment in every HIV-HCV coinfected patient. However, since treatment is not uniformly effective and is associated with side effects in the majority of treated patients, the decision to proceed with treatment requires a careful weighing of risk and benefits for each patient.

Patients should be on a stable ART regimen for at least 3 months prior to starting HCV treatment. Didanosine (DDI) is absolutely contraindicated due to high risk of toxicity.[2] Stavudine (D4T) and abacavir are relative contraindicated due to interactions with ribavirin. AZT increases the risk of anemia and should be avoided if possible.

The treatment of choice is peginterferon alfa (peg-IFN) and weight-based ribavirin (1000 mg daily if <75 kg and 1200 mg daily if >75 kg).[3] Weight-based ribavirin is recommended for all genotypes, due to the higher rate of relapse in HCV-HIV coinfected patients compared with HCV monoinfected patients. The dose of peginterferon alfa-2a is 180 ug weekly and of peginterferon alfa-2b is 1.5 ug/kg weekly. The duration of treatment is 24—48 weeks for genotypes 2 and 3 and 48—72 weeks for genotype 1, 4—6, with the time to loss of HCV determining the length of treatment. Early viral kinetics strongly influences duration of therapy. Shorter duration may be a consideration in patients achieving a rapid virologic response (RVR), defined as undetectable HCV RNA at week 4 of treatment. Longer duration therapy (up to 72 weeks) is a strong consideration in ''slow responders''. The most consistently identified pre-treatment predictors of SVR are HCV viral load and HCV genotype.[4–7] Adherence is an important factor in achieving SVR in HCV-monoinfected patients but data in coinfected patients is more limited. ment using optimal doses and duration of current therapies. The available data indicate that subjects who failed a prior course of suboptimal therapy may achieve SVR but at rates lower than treatment-naive patients.[8] Overall, the chance SVR in previously treated patients is dependent upon the efficacy of the previous tried regimen.

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30.004

Metabolic Abnormalities in HIV Infection

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HIV infected subjects often have a multitude of metabolic defects. The clinical outcomes associated with these abnormalities include lipodystrophy, insulin resistance, dyslipidemia, nonalcoholic fatty liver disease, accelerated atherosclerosis with both coronary artery disease (CAD) and peripheral vascular disease. The development of these complications reflect a complex interaction between the patient, the HIV virus, other concomitant infections and HAART therapy. The seriousness of these complications is underscored by the rising mortality from non-HIV related causes in infected subjects. This is particularly important in males >55 yrs of age where CAD is the leading cause of death. Subjects with HIV infection are at increased risk for myocardial infarction and this risk is related to the use of protease inhibitors (PI). It is however important to note that conventional risk factors e.g. smoking are more important determinants of cardiovascular outcomes rather

than the nature of antiretroviral therapy. It is proposed that changes in adipocyte biology drive these metabolic abnormalities. PIs inhibit CRABP-1 which is required for PPAR-g an adipocyte differentiation factor. They also cause mitochondrial injury. Changes in adipocyte function have also been noted in the absence of PI usage. These lead to either lipoatrophy or lipohypertrophy or differential expression of these phenotypes in the same subject. Lipoatrophy is associated wth leptin deficiency and can be corrected by leptin. Both lipoatrophy and lipohypertrophy are associated with insulin resistance. HIV infected subjects have increased lipolysis secondary to insulin resistance. This is associated with high free fatty acid levels, impaired metabolic clearance of glucose and hyperinsulinemia. These changes lead to the development of nonalcoholic fatty liver disease (NAFLD). NAFLD accelerates progression to cirrhosis in those coinfected with hepatitis C, promotes resistance to anti-HCV therapy, increased cholesterol production and increased predeliction for CAD. PIs increased de novo lipogenesis and also increased HMG CoA reductase while decreasing Cyp7A activity which normally converts cholesterol to bile acids. Dyslipidemia results from both increased lipolysis, decreased clearance of triglycerides and increased cholesterol production. The development of insulin resistance also leads to activation of the innate immune system and an acute phase reaction which creates a systemic proinflammatory, profibrotic state and may activate endothelial cells. Endothelial injury and hyperlipidemia lead to atherosclerosis. PIs block metabolism of mature SREBP-1c and increase its half life thereby increasing the levels of its target CD36. CD36 is expressed on macrophages and promotes cholesterol and lipid uptake thereby creating foam cells and promoting atherosclerosis. To protect subjects from these, the cardiovascular risk can be calculated from Framngham and HIV specific scores. The target LDL cholesterol for those with low risk (<10% over 10 yrs) is 195 mg/dl while that for moderate risk (10—20%) is 155 mg/dl and high risk (>20%) is 105 mg/dl. This is accomplished by attention to traditional risk factors, diet and exercise as well as careful selection of HAART. NNRTI have the lowest while PI have the highest metabolic impact. In those with dyslipidemia, statins and fibrates are first line therapy. Lovastatin and Simvastatin are contraindicated due to drug-drug interactions with HAART. It is important to maintain viral suppression while modulating HAART for dyslipidemia because failure to keep the virus suppressed increases the risk of mortality.

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Orientia tsutsugamushi: a Neglected Pathogen (invited)

31.001

Genome Analysis

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Scrub typhus is caused by the obligate intracellular rickettsia *Orientia tsutsugamushi* (previously called Rickettsia tsutsugamushi). The bacterium is maternally inherited in trombicuid mites and transmitted to humans by feeding larvae. *Orientia* is a member of the Rickettsiales, a genetically diverse group of the alpha-Proteobacteria, include major mammalian pathogens, such as the agents of epidemic typhus, scrub typhus, ehrlichioses and heartwater disease.

Sequenced genomes of this bacterial order have provided exciting insights into reductive genome evolution, antigenic variation and host cell manipulation. The 2,127,051-bp genome of the Boryong strain, which represents the most highly repeated bacterial genome sequenced to date. The repeat density of the scrub typhus pathogen is 200-fold higher than that of its close relative *Rickettsia prowazekii*, the agent of epidemic typhus. A total of 359 tra genes for components of conjugative type IV secretion systems were identified at 79 sites in the genome. Results suggest intragenomic duplications or multiple integrations of a massively proliferating conjugative transfer system. Diversifying selection on host-cell interaction genes along with repeated population bottlenecks may drive rare genome variants to fixation, thereby short-circuiting selection for low complexity in bacterial genomes.

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31.002

Genetic Variability of Orientia tsutsugamushi

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Orientia tsutsugamushi, the agent of the reemerging disease scrub typhus, remains a puzzling microorganism. This alpha proteobacterium, vectorized by thrombiculid mites, has a complex genome containing an exceptionally high repeat density likely resulting from duplication and genome recombination events. It also exhibits a great antigenic diversity, with more than 30 serotypes currently identified, and a geographical specificity of strain distribution. The genetic diversity of O. tsutsugamushi, which is traduced by differences in mortality rates ranging from <1% to 50%, has been the subject of few studies. Most genetic analyses of the population structure of O. tsutsugamushi were based on the study of genes encoding surface-exposed antigens recognized by the immune response of patients. Of these, the 56-kDa protein-encoding gene, unique to O. tsutsugamushi, has been the most extensively studied, representing 70% of all gene sequences available in GenBank for this species. Phylogenetic studies based on this gene identified 6 main clusters (Gilliam, Karp, Kato, Kawazaki, Kuroki, Saitama) but it is likely that more clusters will be described as highlighted by recent studies. When applying the taxonomic criteria used for prokaryotes, the 16S rRNA nucleotide divergence within the O. tsutsugamushi species, as high as 4%, would justify the classification of its isolates in more than one species. In addition, to date, there is no genotyping method that would allow tracing O. tsutsugamushi at the strain level. Such a tool seems essential given the emergence of antibiotic resistant strains. As a consequence, further studies to understand the genetic variability of O. tsutsugamushi are needed and may be performed